

## MEDICINE AND THE MEDIA

# Thyroxine: anatomy of a health scare

A recent change in the formulation of thyroxine replacement therapy caused a dramatic increase in adverse reaction reports in New Zealand—a story widely reported in the media.

**Kate Faasse, Tim Cundy, and Keith Petrie** dissect the health scare

About 70 000 New Zealanders have hypothyroidism and take thyroxine replacement treatment. Since 1973 the only thyroid hormone replacement drug approved and funded by the government for use in New Zealand was the Eltroxin brand, made by GlaxoSmithKline. In 2007 the company moved the manufacture of Eltroxin from Canada to Germany. This resulted in a change in the tablets' inert ingredients: the new formulation differed in markings, size, and colour and—according to some reports—also in taste and rate of dissolution on the tongue. The active ingredient (thyroxine) remained unchanged and continued to be made in Austria.

In 2007 and 2008 New Zealand pharmacies changed to the new formulation of Eltroxin. The old formulation had been used for more than 30 years without problems; but after the new tablets were introduced the rate of adverse event reporting rose nearly 2000-fold—from 14 reports in 30 years to more than 1400 in 18 months. What had happened? And does this incident provide important lessons for future formulation changes and migration to generic drugs?

## Reactions to Eltroxin

Adverse reaction reports relating to the new formulation were first received in October 2007 by New Zealand's Centre for Adverse Reactions Monitoring. By July 2008 294 incidents of adverse reactions had been reported—most (251) reports were received after the Eltroxin formulation change hit the press. The number of adverse reaction reports peaked in September 2008 (at 492). The number fell in October that year to 177 and even further in November to 21, after an announcement that an alternative thyroxine brand was being approved.

About half of all the symptoms reported—such as weight gain, lethargy, muscle pain, joint pain, and depression—can be features of hypothyroidism, but other commonly reported symptoms

are not: conjunctivitis, eye pain, headache, itching, skin rash, abnormal or blurred vision, nausea, and indigestion. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) consulted with local endocrinologists and sought information from the 30 countries in which the new formulation of Eltroxin is used. Some countries reported a small increase in the number of adverse reports, but none had such a dramatic increase as in New Zealand. Medsafe also had independent tests conducted, which found that the new formulation contained the ingredients listed by the company, had the same levels of thyroxine as the old formulation, and was bioequivalent to the old pill.

Medsafe issued press releases to clarify misinformation being spread through the media and internet sites about the new Eltroxin formulation. This misinformation included rumours that the new formulation was being manufactured in India and contained genetically modified ingredients and monosodium glutamate.



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In response to public pressure two additional brands of thyroxine were approved for use in New Zealand in October 2008, enabling patients to switch brands without additional expense. Although these alternatives were provided as soon as they could be, the public perception was that Medsafe's

response to the adverse reactions reporting was too slow, as reflected by demands for immediate action from politicians in a press release headed "How long will Eltroxin sufferers have to wait?" By April 2009 the level of adverse reaction reporting had dropped back to nearly that before the formulation change and has remained low since. There have been very few media stories about the formulation change since November 2008. Despite the negative publicity about Eltroxin, data from Pharmac, New Zealand's drug buying agency, indicate that as at June 2009 many patients had gone back to the drug and that

about 80% of patients using thyroxine were taking the new formulation of Eltroxin.

## Why the rise in adverse reaction reports?

So, was the preparation itself responsible for the adverse effects? Testing had shown that the new formulation was bioequivalent to the older version. Drug bioequivalence is calculated around a group mean, and it is possible that as many as 5% of patients may have experienced an increased or decreased clinical effect from the drug. This could perhaps explain a small proportion of the possible thyroid related symptoms reported, but it is unlikely to explain the majority. So it seems unlikely that the constitution of the medication itself was responsible for the large increase in reported adverse reactions.

## External factors

Pharmac is the agency that manages New Zealand's pharmaceutical budget, by deciding which drugs are to be funded by the government. Shortly before the Eltroxin substitution Pharmac had been under intense media scrutiny because of its decision to ration the drug trastuzumab (Herceptin) for women with early stage breast cancer. The patients' perception, vented on the web and in other places, was that the thyroxine formulation change was another cost cutting strategy by Pharmac. In fact the new formulation was more expensive than the old. But the negative perception and distrust of Pharmac among some of the public are likely to have added to the problems.

## The role of a champion

The champion of the Eltroxin story was Alan Campbell, a pharmacist from Temuka, a small town in the South Island's Canterbury region. Campbell was concerned about patients he had seen having trouble after the formulation change and had publicised these concerns by giving media interviews. He also helped many patients gain access to alternative thyroxine treatments.

Campbell's intervention is likely to have increased the impact of the perceived dangers of Eltroxin, as the public see pharmacists as trusted experts. The role of champions in health scares can help bring issues to the attention of the pub-

lic, but they can also create fear and dissatisfaction that can make situations worse.<sup>1</sup> Stories of a small town health professional taking on the “medical establishment” or a large drug company often appeal to patients and the media.

### Media coverage

The coverage of adverse effects associated with Eltroxin was widespread: on talk radio, television, current affairs magazines and newspapers, and internet news sites.

Among the first reports was one in the *Southland Times* on 7 June 2008, headlined “Changes to drug blamed for illness.” This article and others like it uncritically attributed the symptoms of eye itching, eye pain, depression, nausea, headaches, pain in various body sites, and weight gain directly to the new formulation. One of the country’s major television channels, TV3, ran several stories on the reactions in Eltroxin patients. By the channel’s own admission this coverage is likely to have contributed to the rise in the number of complaints about symptoms. In one major news bulletin on 10 September 2008 Alan Campbell was quoted as saying, “The results are 100% proven that when they go off the Eltroxin on to an alternative their symptoms disappear.”

Differences in the intensity of media coverage of the Eltroxin story also seemed to result in different rates of reporting of symptoms across New Zealand. The Auckland region, where the news media did not particularly focus on the story, is home to around 31% of the New Zealand population but accounted for only 16% of all adverse reactions reported. In contrast 41% of all adverse reaction reports came from the Bay of Plenty, Canterbury, and Southland regions, which together have only 22% of New Zealand’s population. The Eltroxin story was covered extensively in local newspapers in these regions.

Around May and June, when the Eltroxin story was gathering momentum, one of the storylines of the popular medical soap opera *Shortland Street* centred on a drug company manufacturing substandard drugs in India. Serious adverse effects had occurred in hospital patients, and the story culminated in the death of a main character.

In addition, internet based support groups and chat forums were alive with discussion of the formulation change. Rumours that the drug was being manufactured in India, that it contained monosodium glutamate, genetically modified ingredients, and unidentified toxic agents, and that the change was a cost cutting measure all circulated online, as did much suspicion, anxiety, and outrage. “Made in some backwash probably, with hogs and sacred cows meandering in and out of the factory,” read one comment in September 2008. “We are captive subjects. Other countries have choice of what brand they use,”

said another. This misinformation may have influenced beliefs and expectations about the likelihood of experiencing physical symptoms in response to the formulation change and also to the spread of physical symptoms in these patients.

### Patient factors

People with higher levels of emotional distress and anxiety are more likely to attribute physical symptoms to a medical intervention or illness.<sup>2</sup> Hypothyroid patients, even those taking thyroxine replacement therapy, have been found to have greater levels of emotional distress and more physical symptoms than people without hypothyroidism.<sup>3</sup> The formulation change itself is likely to have caused additional anxiety for patients, as the new formulation was the only thyroxine treatment available, and many people were unaware that their pills were going to change.

It seems likely that many patients taking Eltroxin in New Zealand misattributed unrelated physical symptoms to the new formulation. Additionally, symptoms that resulted from possible small differences in bioequivalence may have been misattributed as harmful adverse effects rather than an indication that the dose of thyroxine required re-evaluation.

### Lessons learnt

So, a number of different factors contributed to the Eltroxin health scare. Information about the upcoming formulation change did not reach the majority of patients, and suspicions about the cost cutting motives of Pharmac fed into patients’ concerns about pills that looked different. The adverse reports after the change were picked up by the media, which in turn greatly increased the number of reports. The lack of an available alternative drug, a committed and vocal champion, and the spread of inaccurate information on patient websites also added to patients’ concerns and to complaints about symptoms. That patients were dependent on the treatment provided additional concern and impetus to report symptoms.

As countries look to reduce the cost of health care, reformulations and switches to generic drugs will become more common. Switches provide more opportunities for health scares to develop. Such health scares are costly both for governments and for the patients involved.

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“The benefits of new technologies should also be viewed in the context of what is lost. The demise of some things, say camera film, troubles none but aficionados, the rigid or sentimental of outlook, but other changes are more significant. There is concern that, with an email arriving every three minutes, the modern workforce is permanently distracted and their days fragmented. Universal mobile phone usage means that silence, always a precious commodity, is all but extinct, and with this a chance for reflection and self awareness... Our population feels it is constantly behind, but yet never deserving of a rest... While this technology is undoubtedly transformational, a skill we have yet to learn is when to switch it off.” **Stephen Ginn, trainee psychiatrist, in his Xmas manifesto**



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The first was hearing the response of one patient to being asked how he was after taking only 1 month’s of the 6 months’ treatment for TB. In a loud voice, full of determination and pride, he stated “I was dead, but now you see I am alive.” The second, was seeing the enthusiasm with which some ladies who were patients of the HIV clinic rushed off to football training. While medical care for their HIV was an ongoing part of their lives, they had chosen to form a ladies’ football team to help fight the stigma against HIV that many people face in Zimbabwe.” **Philip du Cros on his work as a TB programme implementer for MSF**

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